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SHORT REPORT

Comprehensive genotype-phenotype correlation in AP-4 deficiency syndrome; Adding data from a large cohort of Iranian patients

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Abstract

Mutations in adaptor protein complex-4 (AP-4) genes have first been identified in 2009, causing a phenotype termed as AP-4 deficiency syndrome. Since then several patients with overlapping phenotypes, comprised of intellectual disability (ID) and spastic tetraplegia have been reported. To delineate the genotype-phenotype correlation of the AP-4 deficiency syndrome, we add the data from 30 affected individuals from 12 out of 640 Iranian families with ID in whom we detected disease-causing variants in AP-4 complex subunits, using next-generation sequencing. Furthermore, by comparing genotype-phenotype findings of those affected individuals with previously reported patients, we further refine the genotype-phenotype correlation in this syndrome. The most frequent reported clinical findings in the 101 cases consist of ID and/or global developmental delay (97%), speech disorders (92.1%), inability to walk (90.1%), spasticity (77.2%), and microcephaly (75.2%). Spastic tetraplegia has been reported in 72.3% of the investigated patients. The major brain imaging findings are abnormal corpus callosum morphology (63.4%) followed by ventriculomegaly (44.5%). Our result might suggest the AP-4 deficiency syndrome as a major differential diagnostic for unknown hereditary neurodegenerative disorders.

KEYWORDS

AP-4 deficiency syndrome, consanguinity, genotype-phenotype correlation, intellectual disability, Iranian families

Hossein Najmabadi and Kimia Kahrizi contributed equally to this study.

